IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT:	Sandra M. Sims	) DOCKET NO.:	3523/2/US
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FILED:	August 20, 2001	) EXAMINER:	Cybille Delacroix-Muirheid

TITLE: SOLUTION COMPOSITION OF AN OXAZOLIDINONE ANTIBIOTIC DRUG HAVING ENHANCED DRUG LOADING

Commissioner for Patents
P.O. Box 1450
U.S. Patent and Trademark Office
Alexandria, VA 22313-1450

DECLARATION BY DR. SANDRA M. SIMS, UNDER 37 CFR 1.131

Sir:

I, Dr. Sandra Sims, declare that:

1. I am an inventor of the above-cited invention.
2. Prior to April 6, 2000, I had conceived and reduced the above-cited invention to practice in the United States, as evidenced by the following:
    a. Prior to April 6, 2000, having earlier conceived of an aqueous composition comprising an oxazolidinone antimicrobial drug in an effective concentration above the practical limit of solubility of the drug, and a pharmaceutically acceptable cyclodextrin compound in a concentration sufficient to maintain the drug in solution at such a concentration, I decided to investigate the feasibility of using one such cyclodextrin, sulfobutylether-β-cyclodextrin (Captisol™) to produce solutions of linezolid with effective concentrations above the practical limit of solubility of the drug.
    b. The results of the study described in (a) above were described in a Study Report, entitled "Feasibility Sudy of using Captisol™ to Lower the Injection Volume of Linezolid Sterile Solution." The report, an internal report, was produced prior to

April 6, 2000. A copy of the Summary page, summarizing the results of the study is attached hereto as an Exhibit.

c, The Summary page clearly shows that we were successful in producing solutions of linezolid containing Captisol™ that were above the practical limit of solubility of linezolid. Specifically, the Summary states that linezolid has a saturation solubility at ambient conditions of 2.9 +/- j0.1 mg/ml, and we produced solutions with concentrations of linezolid of 4.3, 9.5, 15.9, 22.1, 33.4, and 59.9 mg/ml, respectively.

3. I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further, that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both under Section 1001 of Title 18 of the United States Code and such willful false statements may jeopardize the validity of an application or any patent issuing thereon.

Sandra M. Sims — 3 Nov. 2003

Dr. Sandra M. Sims — Date

Exhibit to 131 Dec

2 SUMMARY

This report investigated the feasibility of using sulfobutylether-β-cyclodextrin (Captisol™), a solubilizing compound manufactured by CyDex, to obtain a convenient volume for linezolid intravenous administration, i.e., 100 ml or less for a 600 mg dose. The clinical and market formulation for Linezolid Injection is a 2 mg/ml sterile solution of linezolid citrate-buffered at pH 4.8. This formulation is packaged in 100, 200 and 300 ml Excel® infusion bags. These large volumes can be problematic for patients with a history of hypertension, cardiac and/or renal problems. In addition, large volume parenterals are typically more expensive, more difficult to manufacture and more difficult to handle in the clinic when compared to small volume parenterals packaged in glass vials or ampules.

The saturation solubility of linezolid at ambient conditions is 2.9 ± 0.1 mg/ml. The solubility of linezolid was measured in 1, 5, 10, 15, 25 and 50% aqueous Captisol™ solutions and found to be 4.3, 9.5, 15.9, 22.1, 33.4 and 59.9 mg/ml, respectively.

The slowest degradation rate of linezolid in constant ionic strength citrate-phosphate buffers (0.5 M) was between pH 4 to pH 4.8, with Captisol™ having no significant effect on the degradation rate profile. However, it was visually noted that the solutions without Captisol™ turned yellow to amber color much faster than solutions with Captisol™. Further testing at 70°C showed that the chemical stability of linezolid was not significantly affected by the presence of Captisol™ (5% and 10%) in typical formulations consisting of isotonic, 10 mM citrate buffer solutions at pH 4.5. An isotonic formulation consisting of 8 mg/ml linezolid in 10% Captisol™ (75 ml/dose) was physically stable at 25°C and at a refrigerated temperature for the duration of the study, i.e., 2 months. A cost analysis of possible formulations showed that this formulation would range between $5.75 and $10 per 600 mg dose (excluding costs for terminal heat sterilization), primarily due to the high cost of Captisol™ (currently $1000/kg).

This study showed that Captisol™ improved the solubility of linezolid sufficiently to prepare 600 mg doses in volumes less than 100 ml. Also, Captisol™ had no significant effect on the degradation rate profile of linezolid or in the appearance rate of degradation impurities. This study did not address Captisol™ safety or blood compatibility of the formulations. It remains to be determined if the advantages of low volume and photodegradation protection offsets the disadvantage of increased cost of goods.